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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/809,745	03/15/2001	Howard L. Weiner	B0801/7202 (AWS)	5345

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EXAMINER	
LIU, SAMUEL W	

ART UNIT	PAPER NUMBER
1653	

DATE MAILED: 03/30/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/809,745	WEINER ET AL.	
	Examiner	Art Unit	
	Samuel W Liu	1653	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *05 February 2004*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-11,19,25,31 and 44* is/are pending in the application.

4a) Of the above claim(s) *25 and 44* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-11,19 and 31* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *6-11-01*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Status of the claims

Claims 1-11, 19, 25, 31 and 44 are pending.

Applicants' amendment filed 5 February 2004, which amends claims 1, 11, 19, 31, and applicants' request for extension of time of one month have been entered. cancels claim 23 has been entered. Note that claims 12-18, 20-24, 26-30, 32-43 and 45-55 were previously canceled by applicants' amendment filed 29 May 2001, that claims 25 and 44 was withdrawn from the further consideration.

The following Office Action is applicable to the pending claims 1-11, 19 and 31.

Please note that grounds of objection and/or rejection not explicitly restated and/or set forth below are withdrawn.

IDS

The references listed in IDS filed 11 June 2001, have been considered.

Claim Rejections - 35 USC § 112, the second paragraph

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter that the applicant regards as his invention.

Claims 1-11, 19 and 31 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 1 is unclear in "HSP60/65"; does it refers to HSP60 fusion with HSP65? The dependent claims are also rejected.

Claims 1, 11, 19 and 31 recitation of "peptide analog of isolated HSP60/65" (amended) is indefinite because the specification does not define what the peptide analog of isolated HSP60/65 heat shock protein is, and the recitation is unclear as to whether or not the said analog encompasses any fusion of the said protein, or protein mimetic thereof. The dependent claims are also rejected.

Applicants' response to the rejection under 35 USC 112, the second paragraph

The response filed 5 February 2004 asserts that the specification has provides the definition for the "analog" which is referred to pages 22-23; thus, claims 1-11, 19 and 31 are not indefinite (see page 9 of the response). The applicants' argument is unpersuasive because the reason set forth in the above rejection and the following. The pages 22-23 of the specification set forth that the term "analog' encompasses any compounds that structurally related to the heat shock protein (HSP); however, the specification does not define what the "peptide analog" of said heat shock protein is. Neither the specification nor the instant claims make it clear that (i) whether or not said analog (a *generic term*) encompasses organic compound-conjugated protein or HSP protein mimetic or an engineered biopolymer comprising HSP60 or HSP 65 or the fragment(s), e.g., HSP-nucleoprotein fusion (see *Anthony, L. S.* et al. (2000) 17, 373-383). Thus, the applicants' argument is deemed unpersuasive.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1, 11, 19 and 31 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. The specification as originally filed does not provide support for the invention as now claimed.

This is a New Matter rejection for the following reasons:

The amended claims 1, 11, 19 and 31 recite "peptide analog of an isolated HSP60/65" which represents a departure from the specification and the claims as originally filed.

Applicant's amendment filed 1 December 2003 asserts that no new matter is introduced (see page 8, the 1st paragraph). However, the specification does not provide a clear support of the above-stated claim recitation "peptide analog of an isolated HSP60/65". The instant claims now recite limitations which were not clearly disclosed in the specification and claims as filed, and now change the scope of the instant disclosure as filed. Such limitations recited in the present claims, which did not appear in the specification or original claims, as filed, introduce new concepts and violate the description requirement of the first paragraph of 35 U.S.C. 112.

Claims 1-7, 11, 19 and 31 are rejected under 35 U.S.C. 112, first paragraph, because the specification, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The specification does not describe a method of treating or suppressing a vascular disorder sate comprising administering to a subject a composition comprising a peptide analog of

the HSP60 or/and HSP65. Thus, Applicants are not in possession of the claimed method indicated above.

The specification only teaches the method for treating or suppressing a vascular disorder sate comprising administering to a subject a composition comprising an isolated HSP60 or HSP65 protein.

One of skill in the art would reasonably conclude that the disclosure fails to provide a representative number of the peptide analog encompassing any fusion biopolymer or peptide mimetic comprising a portion or full-length HSP protein thereof, and fails to describe the biological activities of said analog receptor), and thus fails to provide written description regarding their therapeutic use for treating or suppressing a vascular disorder sate. Thus, applicants were not in a possession of the claimed method thereof

Applicant is directed to the Revised Interim Guidelines for the Examination of Patent Applications Under the 35 U.S.C. 112, ¶ 1 "Written Description" Requirement, Federal Register, Vol. 66, No. 4, pages 1099-1111, Friday January 5, 2001.

Claims 1-7, 11, 19 and 31 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a process of treating a vascular disorder in a mammal comprising administering to a subject composition comprising HSP60 or HSP65, does not enable using any peptide analog of HSP60 or HSH60/65 in the claimed method. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

The application disclosure and claims have been compared per the factors indicated in the decision *in re* Wands 8 USPQ2d 1400, 1400 (Fed. Cir. 1998). These factors are considered when determining whether there is sufficient evidence to support a description that a disclosure does not satisfy the enablement requirement and whether any necessary experimentation is undue. The factors include but not limited to: 1) the nature of the invention; 2) the breath of the claims; 3) the predictability or unpredictability of the art; 4) the amount of direction or guidance presented; 5) the presence or absence of working examples; 6) the quantity of experimentation necessary; 7) the relative skill of those skilled in the art.

Each factor applicable is addressed below on the basis of comparison of the disclosure, the claims and the state of the prior art in the assessment of undue experimentation.

(1) The scope of the claims/(2) The nature of the invention:

Claims 1, 19 and 31 set forth that the composition used in the claimed method comprises a peptide analog of an isolated HSP60 or HSP65. Yet, the specification provides insufficient description and working examples as to treating a vascular disorder using a composition comprising said peptide analog. Note that the peptide analog would encompasses the following the HSP analog (structural **or** functional analog) (i) peptide mimetic (see page 23, the 1st paragraph of the specification) which can be peptide derivative wherein the HSP60 or HSP65 or fragments(s) thereof is conjugated with an organic compound; or (ii) a fusion biopolymer comprising said HSP protein; or (iii) any compounds (compositions) that functionally mimic inflammatory response-suppressive activity of heat shock protein (see the specification at page 23, the 1st paragraph).

Note that claim 1, 19 and 31 as written are directed to use of the above mentioned HSP analog for treating a vascular disease.

As structural analog is concerned, because the specification does not provide working examples or/and teaching as to the peptide mimetic (analog) or fusion biopolymer comprising HSP60 or/and HSP65, the skilled artisan cannot envision all the contemplated peptide analog possibilities which are structurally divergent from unmodified HSP molecules, and would not know how to make and use the HSP analog(s) to formulate the composition comprising the said peptide analog and use the composition thereof for treating a vascular disorder.

As functional analog is concerned, make and use of the peptide analog is highly unpredictable. The following two issues are considered.

(**1**) HSP encompasses a growing number of proteins including five conserved classes: HSP100, HSP90, HSP70, HSP60 and the small heat-shock proteins (sHSPs) (see Kim, K. K. et al. (1998) *Nature*, 394, 595-599). It has been known that HSP90 participates in suppressing inflammatory response vai interacting with steroid hormone (e.g., glucocorticoid hormone) receptor (see *Padgett, D. A.* et al. (2003) *Trends in Immunol.* 24, 444-448). Because of this inflammatory response suppressive effect of HSP90, the HSP90 protein is considered as a functional mimetic of the claimed composition of this application (see the above statement). Therefor, the claimed peptide analog would encompass a fusion protein between HSP90 (but NOT HSP65 or HSP60) and a heterologous sequence.

(**2**) Furthermore, *Padgett et al.* also teach that substance P is able to reduce inflammatory response; thus, non-HSP factor, *e.g.*, the substance P should also be encompassed in the above-said functional analog (mimetic). Yet, the specification does not exemplify and teach the substance P but HSP65 and HSP65 activity of surprising a vascular disorder. Thus, the current disclosure is not enabling for using any peptide analog that is a functional analog of the claimed HSP65 or

HSP65. Therefore, the scope of claims is outside the bounds of the enablement and would have resulted in the necessity of undue experimentation.

(3) The unpredictability of the art:

The claimed invention is directed to a vast number of the variant (analog) HSP molecules, which include any mutants (genetically or/and recombinantly or chemically generated), non-proteinous HSP derivatives, or any protein mimics of HSP. The specification provides not teaching or guidance as to how to make, characterize and use the variants thereof. Thus, the skilled artisan would not know how to make, characterize and use the variant HSP. As a result, outcome of the method of treating a vascular disorder comprising administering the composition comprising the HSP variant thereof are unpredictable.

The instant application describe HSP65 fragment at pages 11-12. Yet, the specification proved insufficient guidance and no working examples as to the fragment of an isolated HSP60/65 (see claims 1, 11, 19 and 31). As written in the claims 1, 11, 19 and 31, fragment appears to encompass fusion polypeptide comprising HSP60 or fragment thereof and HSP65 or fragment thereof. The specification teaches neither structure nor function of the said fusion polypeptide fragment. Applicant has disclosed only how to use full-length HSP65 (see Figures 2-5 and examples 1-3) for the claimed method. The skilled artisan cannot envision all the contemplated possibilities of HSP60 and HSP65 analogs (including the fragments thereof). Theses analogs are structurally and/or functionally divergent from unmodified HSP molecules, e.g., fusion biopolymer comprising said HSP protein and heterologous sequence(s). Consequently, conception cannot be achieved until a representative description of the structural and functional properties of the claimed invention has occurred, regardless of the complexity or simplicity of the method. Therefore,

unpredictability of the claimed method comprising use of a HSP65 or HSP60 or analog molecule thereof is exceedingly high.

(4) The state of the prior art:

The general knowledge and level of skilled in the art do not supplement the omitted description because specific, not general, guidance is what is needed. Since the disclosure fails to describe common attribute and characteristics that identify any pharmaceutical agent qualified for treating a vascular disorder. As stated above, the current claim language: a peptide analog is a generic term which encompasses any variants of any structural or/and functional modifications. Because the genus is highly variant, the specification needs to provide sufficient guidance to be considered enabling.

(5) The quantity of experimentation necessary:

In the absence of working examples with regard to the genus stated above, unpredictability of the art, the lack of sufficient guidance in the specification and the breadth of the claims, it would take undue trials and errors to practice the claimed invention. The quantity of experimentation would be large and unpredictable. One skilled in the art would be required to carry out an undue experimentation for screening and characterizing the HSP peptide analog molecules that have pharmaceutical activity against vascular disorder state.

(6) The relative skill of those in the art:

The general knowledge and level of skill in the art do not supplement the omitted description with respect to a massive number of variant sequences of peptide. In view of the preceding factors (1-5), the level of skill in this art is high and requires at least a molecular biologist with several years of experience in mutagenesis, protein engineering as well as

knowledge in HSP biochemistry, pathology and pharmacology. Yet, even with a level of skill in the art as those mentioned in precedence, predictability of the results is still highly variable. An unduly level of skill is needed for the skilled artisan in order to identify the useful HSP molecule, which is selected from the five HSP classes and functionally characterized for its efficacy of treating a vascular disorder.

In consideration of each of factors stated above, absent factual data to the contrary, the amount and level of experimentation needed is undue.

Applicants' response to the rejection under 35 USC 112, the first paragraph

The response filed 5 February 2004 discusses the issue reading enablement of argument of the HSP65 fragment; and based on this, the response asserts that the instant amendment to the claims is enabling for the claimed method using the peptide analog of an isolated HSP60/65 (see page 10). The applicants' argument has been fully considered but it is unpersuasive because of the reason stated in the above stated ground of rejection and the following reasons.

Note that said fragment recited in the instant claims appears to be a fusion peptide between HSP65 and HSP60, which is therefore not supported by the enablement (also see the statement *supra*). The presently claimed peptide analog encompasses any peptide mimetics or any fusion biopolymers comprising HSP60 or/and HSP65 or fragment(s) thereof (see the statement *supra*). The peptide analog is neither supported by written description nor by the enablement. The generic phrase "peptide analog" reads on functional analog of HSP65 or HSP60, which encompasses any non-HSP protein or any biomolecule as long as it has ability of mimicking inflammatory response-suppressive activity of heat shock protein (see the specification at page 23, lines 6-7). Therefore,

the current claim language "peptide analog" renders that the scope of claims is outside the bounds of the enablement and would have resulted in the necessity of undue experimentation.

The claim rejections - 35 USC §103is withdrawn in light of the applicants' amendment to the claims.

Conclusion

No claims are allowed.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a). A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Samuel Wei Liu whose telephone number is 571-272-0949. The examiner can normally be reached from 9:00 a.m. to 5:00 p.m. on weekdays. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Dr. Christopher Low, can be reached on 571-272-0951. The fax phone number for the organization where this application or proceeding is assigned is 703 308-4242 or 703 872-9306 (official) or 703 872-

9307 (after final). Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703 305-4700.

S.W.L

Samuel Wei Liu, Ph.D.

March 15, 2004

Karen Cochrane Carlson

KAREN COCHRANE CARLSON, PH.D
PRIMARY EXAMINER